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Sentinel Lymph Node in Colorectal Carcinoma

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ABSTRACT

Background: Metastasis to the regional lymph nodes is an important prognostic factor in colorectal cancer and nodal evaluation is essential for accurate staging. Sentinel lymph node (SLN) mapping is an additional method for improving colorectal cancer nodal staging.

Objective: To evaluate the identification of SLN sensitivity and accuracy of nodal staging, its upstaging benefits and pattern of nodal metastases in colorectal carcinoma.

Patients and Methods: Lymphatic mapping was performed using patent blue in sixty patients with histopathologic diagnosis of colorectal carcinoma. Enhanced pathologic examination was carried out on (SLNs) using Haematoxylin & Eosin and immunohistochemistry.

Results: The patients studied had an average tumor size 6.6 cm and rectal tumors represented 43.3% of the group. Colon tumors had SLN identification rate of 94.1%, while rectal tumors had 80.8%. Overall, SLN mapping accuracy was 75.4%, sensitivity 66.7% and 33.3% false negative rate. Upstaging rate was 10.5%. No aberrant lymphatic drainage could be detected in our patients.

Conclusion: Intraoperative SLN mapping technique is feasible, safe, accurate, and has no apparent side effects. Implications for long-term survival and prognosis need to be further evaluated in additional studies.

Keywords: Sentinel lymph node (SLN), Colorectal carcinoma, Lymph node mapping.

INTRODUCTION

Metastasis to regional lymph nodes is one of the most important factors relating to prognosis of colorectal carcinomas and the information on nodal involvement is an important part of all major colorectal carcinomas staging systems. Patient with metastatic lymph nodes have shorter survival and may require adjuvant systemic chemotherapy [(1)]. Even with successful surgical intervention, approximately 20-25% of stage II colorectal carcinoma patients develop regional or distant metastases within 5 years of diagnosis [(2)], presumably owing to pathological understating from missed micrometastases in lymph nodes [(3)]. Pathologic techniques, such as immunohistochemistry can identify micrometastases disease in lymph nodes. However, it is cost-prohibitive and highly time-consuming to ultrastage all the nodes in a given specimen, especially when the specimen contains multiple nodes [(4)].

SLN biopsy has been found to be highly effective in correctly predicting the nodal status for melanoma and breast cancer patients [(5)]. In contrast, the current evidence for sentinel lymph node biopsy (SLNB) in colorectal cancer is conflictive. On the other hand, there are few study groups, who reported a high predictive value of SLNB for nodal status [(6, 7)], hypothesized an improved staging by detection of small tumor deposits as well as increased yield of harvested lymph nodes [(8, 9)] and reported significant percentage of aberrant lymphatic drainage outside the planned resection margins [(10)]. On the other hand, several recent studies could not confirm these results [(11, 12)].

PATIENTS AND METHODS

Prospective study of 60 patients with histopathologic diagnosis of colorectal carcinoma admitted to the Surgical Oncology Department at the National Cancer Institute (NCI), Cairo University, Cairo, Egypt in the period from 2006 till 2012.

The patients included in the study were 27 males and 33 females with an average age of 54 years (ranging from 19 to 74 years).

Eligibility criteria: Histopathologic evidence of colorectal carcinoma, absence of distant metastases, absence of previous colorectal or major abdominal surgery, and physical fitness for surgery.

Preoperative evaluation:

History: Age, sex, occupation and smoking. Complaint of the patient: history of present illness, onset, course and duration of the complaint. Past history: history of previous operations, and family history.

Clinical examination: General and local examination of the patient is important to exclude any previous major abdominal surgeries or distant metastases.

Investigations:

- Laboratory: Routine investigations included CBC, liver function tests, blood sugar, coagulation profile and carcino-embryonic antigen (CEA).
- Radiology: Chest x-ray and CT abdomen and pelvis with oral and IV contrast.
- Endoscopy: Colonoscopy for entire colon to evaluate the site, size, shape and extent of the primary lesion with biopsies from the primary lesions and other suspicious lesions in the colon.

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- Metastatic work up was done to exclude any distant metastases.

Preoperative preparation:

- Mechanical and chemical colonic preparations were started three days before operation.
- Treatment of any chest infection and control of blood sugar in diabetic patients and blood pressure in hypertensive patients.

Intra-operative methods:

After opening the abdominal wall, the minimal number of surgical procedures necessary to reach the tumor site was performed. Subsequently, 1-2 ml of vital dye (patent blue) and/or 0.5-1mci of technetium labeled human serum albumin (radioactive colloid) were injected subserosal around the tumor in colon and high rectal carcinoma cases and submucosal in low rectal cancer cases, taking care to prevent dye leakage into surgical field and bowel lumen. Within 5-10 minutes, blue staining of the lymphatic vessels reach one or more nodes (the sentinel lymph nodes), which were localized and extracted as a separate biopsy. Subsequently, standard colon resection with complete lymphadenectomy was adopted.

Pathological processing:

Pathologic analysis of the specimens included microscopic examination of invasion, histologic grade and distal margin of the tumor. All lymph nodes were dissected from the surgical specimen and fixed in formalin. Each SLN greater than 3 mm was bivalve or serially cut between 2 to3 mm along the transverse plane to have the widest surface. All lymph nodes were submitted in their entirety. The entire specimen was then dissected in a standard fashion and fixed in formalin. Three 5 µm slices were cut from the paraffin-embedded tissue of the SLN at a 1.5 µm interval and stained with Hematoxylin and Eosin. One of the representative sections was immunostained for the demonstration cytokeratin (Clones AE1/AE3, Dako LSAB system).

All SLNs that contained any cell consistent with a malignant morphology and confirmed by cytokeratin immunostain were considered pathologically positive. Metastatic foci were measured by using an Olympus eye piece micrometer and classified according to the TNM staging scheme as (1) isolated tumor cells (ITCs) of 0.2 mm or smaller; (2) micrometastasis larger than 0.2 mm but not greater than 2 mm, and (3) macrometastasis larger than 2 mm. All lymph nodes were dissected and primary tumors were examined as in routine histological examination. Pathologic analysis of the primary tumor included assessment of tumor stage, histological grade and distal margin of the tumor.

Ethical approval:

An approval of the study was obtained from Cairo University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical methods

Data were analyzed using SPSS win statistical package version 17 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Correlations: Detection rate refers to the number of times a sentinel node was actually identifiable = (Number of successful attempts to retrieve a sentinel node/Number of attempts to retrieve a sentinel node) 100 (%). Sensitivity refers to the number of times the sentinel node reflects the fact that disease is present in the non-sentinel nodes = (Number of patients with tumor-involved sentinel nodes/Number of patients with any lymph node containing tumor) 100 (%). The false negative rate reflects the proportion of patients in whom no cancer was identified in the sentinel node but who had nodal deposits found in their non-sentinel nodes compared to the total number of those who had tumor containing metastases in non-sentinel nodes = (Number of false negative patients/Number of true positive cases + number of false-negative cases) 100 (%). Negative predictive value: Number of nodal negative patients/ Number of nodal negative patients+ number of false negative results x 100 (%). Accuracy rate refers to the ability of the sentinel node to reflect the overall status of the lymph basin (whether positive or negative) = (Number of correct predictions of the nodal status by sentinel node biopsy/Number of patients undergoing sentinel node biopsy) 100 (%).

Upstaging rate refers to the number of cases in which sophisticated analysis of the sentinel node reveals tumor deposits that otherwise were not detected = (Number of patients revealing micrometastases or isolated tumor cells in the sentinel node/Number of patients classified as N0 after routine histopathologic examination) 100 (%.

RESULTS

Sixty patients were enrolled in this study, number of male patients was 27 (45%) and female patients were 33 (55%). The mean age was 54 years old ranging from (19-74) year old.

Tumor site: The site of the tumor was distributed as follows: lesions at the caecum were found in 6 cases (10%) of cases, ascending colon lesions in 7 cases (11.7%), transverse colon lesions in 8 cases (13.3%), descending colon lesions in 5 cases (8.3%), sigmoid colon lesions in 8 cases (13.3%) and rectal lesions were found in 26 cases (43.3%) of cases.

Tumor pathology: In our study, pathologic type of the tumor was mainly adenocarcinoma of which 46% were glandular adenocarcinoma, 3% signet ring and 11%

were mucinous adenocarcinoma. The grade of the tumor ranged from grade 1 to grade 3: 10% (6 pts) were grade 1, 80% (48 pts) were grade 2 and 10% (6 pts) were grade 3.

Tumor Staging:

The pathological staging of the tumor in our study according to the TNM system following American Joint Society of Caner was as follows: 13 patients (21.7%) were T2, 40 patients (66.7%) were T3, and 7 patients (11.7%) were T4. the mean size of the tumor in our study was 6.6 cm ranging from 2-15 cm.

Resection margins:

We categorize the margin of resection in our study into 2 categories: Radial margin and mucosal margin. Out of 60 patients, 56 pts (93.3%) had negative radial margin and only 4 patients (6.7%) had positive radial margin. Regarding mucosal margin, 59 patients (97.3%) had negative mucosal margin and only one patient (1.7%) had positive mucosal margin. The mean of the least mucosal margin was 5.4 cm ranging from 5-22 cm (Table 1).

Table (1): Distribution of patients according to sex, tumor site, tumor type, tumor grade, tumor stage, radial margins and mucosal margin

	Frequency	Percent
Sex:		
Male	27	45%
Female	33	55%
Site:		
Caecum	6	10%
Ascending colon	7	11.7%
Transverse colon	8	13.3%
Descending colon	5	8.3%
Sigmoid colon	8	13.3%
Rectum	26	43.3%
Tumor type:		
Glandular	46	76.7%
Signet ring	3	5%
Mucinous	11	18.3%
Tumor grade:		
G1	6	10%
G2	48	80%
G3	6	10%
Tumor stage:		
T1	13	21.7%
T3	40	66.7%
T4	7	11.7%
Radial magin:		
-ve	56	93.3%
+ve	4	6.7%
Mucosal margin:		
-ve	59	98.3%
+ve	1	1.7%
Total	**60**	**100%**

Sentinel Lymph Nodes (SLNs): The mean number of dissected lymph nodes was 15.5, ranging from 2-42 lymph nodes. The mean number of sentinel lymph nodes (SLN) detected was 1.6, ranging from 1-5 lymph nodes and the mean number of non- sentinel lymph nodes (non SLN) was 14.4, ranging from 1-41 (Table 2).

Table (2): Different numeric values

	Count	Mean	Standard Deviation	Median	Minimum	Maximum
Age	60	54.0	12.4	54.5	19.0	74.0
Tumor size	60	6.6	2.6	6.0	2.0	15.0
MM-size-cm	60	5.4	5.1	4.0	0.5	22.0
Total-LN-no	60	15.5	8.1	13.5	2.0	42.0
No-SLN	60	1.6	0.9	1.0	1.0	5.0
Non-SLN-no	60	14.4	8.3	12.0	1.0	41.0
Size-SLN-(cm)	60	1.0	0.4	1.0	0.5	2.0

In our study, we could identify the SLN in 53 patients (88.3%) while in 7 patients (11.7%), no SLN was identified. The detection rate was calculated by this equation: Detection rate = (53/60) X 100 = 88.3% (Table (3).

Table (3): Identification of SLN

	Frequency	Percent
Not identified	7	11.7
Identified	53	88.3
Total	60	100.00

We could identify (SLN) in 32 pts out of 34 pts with isolated colonic cancer cases representing 94.1% detection rate. In isolated rectal cancer cases, we could identify SLN in 21 patients out of 26 patients, representing 80.8% detection rate (Table 4).

Table (4): Identification of SLN according to tumor site

			Tumor - site1		Total
			Rectum	Colon	
Identification of SLN	**Not identified**	**Count**	**5**	**2**	**7**
		% within tumor-site1	**19.2%**	**5.9%**	**11.7%**
	Identified	**Count**	**21**	**32**	**53**
		% within tumor-site1	**80.8%**	**94.1%**	**88.3%**
Total		**Count**	**26**	**34**	**60**
		% within tumor-site1	**100.0%**	**100.0%**	**100.0%**

The mean size of detected SLN was 1cm ranging from 2-5 cm. In 38 cases (71.7%) out of 53 cases the SLNs were negative, and were positive in 15 cases (28.3%) out of 53 cases by examination of Haematoxylin & Eosin (H & E) stained slides. In the H & E negative cases, Immunohistochemical examination (IHC) by cytokeratin revealed 4 (10.5%) cases positive for presence of tumor cells and 34 (89.5%) were negative. The number of positive SLN cases by H & E and IHC were 19 (35.8%) of cases (Tables 5 and 6).

Table (5): Status of SLN by H & E

	Frequency	Percent
-ve	38	71.7%
+ve	15	28.3%
Total	53	100.00%

Table (6): Status of SLN by IHC

Frequency	Number	Percent
-ve	**34**	**89.5%**
+ve	**4**	**10.5%**
Total	**38**	**100%**

About non-SLN status, 35 (66%) cases out of 53 were negative and 18 (34%) out of 53 cases were positive. The comparison between SLN and non were as follows in table (7).

Table (7): Comparison between SLN and Non SLN status

			Non -SLN -	status	Total
			-ve	+ve	
Status-SLN	**-ve**	**Count**	28	6	34
	+ve	**O% of total**	52.8%	11.3%	64.2%
		Count	7	12	19
Total		**O% of total**	13.2%	22.6%	35.8%
		Count	35	18	53
		O% of total	66.0%	34.0%	100.0%

Accuracy rate = 52.8% + 22.6% = 75.4%, (28+12) /53) *100 = 75.4%.
Sensitivity = (12/18) * 100 = 66.7%.
The false negative rate: False - ve rate = (6/18) * 100% = 33.3%.
Negative predictive value: Negative predictive value = (28/34) * 100 = 82.4%.
Upstaging rate: Upstaging = (4/38) * 100 = 10.5%.

DISCUSSION

Tumor staging at the time of initial diagnosis is the most important prognostic factor in patients with colorectal cancer [(13)]. Complete regional en-bloc lymphadenectomy followed by pathologic H & E nodal evaluation remains the most widely practiced staging method [(14)]. The presence of lymph node metastases decreases the 5-year survival by approximately 20% to 30% [(7)]. Patients without evidence of metastatic nodal involvement are staged I or II according to the AJCC [(15)]. Unfortunately, 20% to 30% of stage I or II patients with colon cancer die from local recurrence or distant metastases within 5 years of diagnosis [(16)]. A likely explanation for this high mortality rate is that conventional methods underdiagnose micrometastatic nodal involvement. Therefore, alternative diagnostic techniques need to be developed in order to better identify patients at risk. Various methods have been studied in order to enhance the detection of micrometastases. These include fat-clearing techniques, serial sectioning of lymph nodes [(17)], immunohistochemical staining and reverse transcriptase PCR [(18)]. However, all these techniques are expensive and time consuming if performed on all lymph nodes obtained from the surgical specimen. It is in this scenario that SLN mapping plays a significant role. The SLN concept is based on an orderly progression of tumor cells, in a stepwise fashion, from the primary site through organized lymphatic channels into the regional lymph nodes. This process has been validated in patients with melanoma [(19)].

Once the SLN has been identified, a dedicated cost-effective evaluation of the SLN can be performed. If there is a high rate of SLN identification, and if the status of the SLN accurately predicts the metastatic involvement of the nodal basin, then the SLN mapping would be a very useful technique. This has been documented in melanoma and breast cancer patients[(20)].

Use of the SLN technique in patients with colorectal cancer in previous studies have shown that 5% to 21% of patients are upstaged from stages I and II to stage III disease [(21, 22)]. Nodal micrometastases were identified in patients when multisectioning and immunohistochemical evaluation of the SLNs were performed [(22, 23)]. These results are co-related to current study where the SLN was the only node containing metastatic disease in 7 patients (13.2% of patients), and the SLN and immunohistochemical stains upstaged 10.5% of all patients by demonstrating micrometastatic involvement. Some authors believe as these patients are upstaged from AJCC stage I or II to stage III, additional adjuvant chemotherapy should be strongly considered. Whether such therapy prolongs the survival of these patients with micrometastases remains the point of further assessment [(7)].

A valuable benefit of SLN mapping technique is the ability to recognize aberrant lymphatic drainage, which has been reported in 2 to 8% of cases of rectal cancer [(24, 25)]. Although there were no such cases in the current study, we believe that if aberrant lymphatic drainage is identified, a more radical surgical resection and lymphadenectomy should be performed in order to achieve complete tumor excision. Whether missed aberrant drainage is a significant source of inadequate staging. Therefore, higher tumor recurrence rates, lower response rates to adjuvant therapy, and decreased overall survival, still needs to be evaluated by future studies.

The concept of SLN mapping, as being a less invasive alternative to formal lymphadenectomy, as it may be for melanoma and breast cancer patients, may not be correct for colon cancer [(22)]. In colon cancer, formal lymphadenectomy is still required in conjunction with the SLN technique, as a high percentage (22.6% in current study) of patients with positive SLN have other positive lymph nodes. Additionally, it is not possible to ensure that a SLN is negative at the time of surgery, as frozen section may be inaccurate and some nodes can only be found positive on immunohistochemical staining, which is not available at the time of the operation.

In the current study, SLNs were identified in 88.3% of patients. This is certainly lower than the reported 92% and 98% rate by **Bertagnolli *et al.*** [(11)]

and **Bilchik *et al.* [26],** but still higher than detection rates detected by another authors 82% and 85% [22, 24]. Certain factors may have accounted for the lower detection rate. These include injection of dye into the intestinal lumen instead of subserosal. Failure to perform a completely circumferential injection around the tumor, large tumors that may require more dye in order to achieve complete peritumoral injection, and some nodes being completely replaced by tumor, which obstructs the lymphatic flow and prevents adequate nodal staining.

In the current study identification rates in rectal cancer cases was 80.8% as in vivo sentinel lymph node mapping in rectal cancer with blue dye is technically difficult because of the anatomic location of the rectum deep within the narrow pelvis. A clear view of the tumour site is therefore not always feasible. Some authors used patent blue exclusively as the staining dye. The accuracy of this agent when used alone has been validated in melanoma and breast cancer patients [27]. However, because these patients may have abnormal areas of lymphatic drainage that may go undetected, some centers have added the use of radioactive colloid in an attempt to further improve the SLN identification rate [28, 29].

The sensitivity of the SLN in colorectal carcinoma varies in the literature between 54% in the study of **Bembenek *et al.*** [22] and 74–89% in the study of **Bilchik *et al.*** [26], and **Saha *et al.*** [28]. In current study the sensitivity was 66.7% , which is comparable to other results.

The smallest false-negative rate was achieved by **Bilchick *et al.*** [26] (7.4%), but other authors reported a significantly higher rate of false-negative results (46% for colon cancer in the study of **Bembenek *et al.*** [22], 43% in rectal cancer in the study of **Baton *et al.*** [30]. In current study we had relatively high false negative rate 33.3% but still comparable with the result of other centers. The cases of false negative staging we observed might be due to the following scenarios: (i) Obstruction of lymphatic ducts by tumors. (ii) Sampling errors during pathologic examination. (iii) Procedure faults and/or errors in injecting the blue dye (injection is very important for the correct visualization of the SLN).

This false negative phenomenon, however, is not as dangerous for down staging as in other tumors, as classic resection is always performed. The greatest impact on staging is not the presence of ectopic SLNs, but the thorough examination of the SLN using special staining methods.

CONCLUSION

Intraoperative SLN mapping technique is feasible, safe, accurate, and has no apparent side effects. Implications for long-term survival and prognosis need to be further evaluated in additional studies.

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